REMARKS

After entry of the foregoing amendments, claims 23-33 will remain pending. Claims 1-22 are canceled herein, without prejudice. Claim 23 is amended to more clearly define the invention. Claim 23 has been amended to clarify that the method for quantifying molecules expressing a selected epitope in a sample comprises immobilizing a molecule expressing a selected epitope in a sample to a selected surface, contacting the surface with an epitope detector so that the epitope detector binds to immobilized molecules on the surface, wherein said epitope detector comprising an oligonucleotide attached to a monoclonal antibody for the selected epitope, a single chain Fv for the epitope, a constrained epitope specific CDR, a CDR mimetic, or an engineered CDR, wherein said oligonucleotide comprises an RNA promoter, amplifying the oligonucleotide of said epitope detector by RNA amplification to produce an amplified RNA product *that is not labeled with a radioactive label or a fluorescent label*, contacting the amplified RNA product with a fluorescent dye which stains the amplified RNA product, and measuring a quanta of fluorescent signals emitted from the stained amplified RNA product which is directly proportional to epitope detector bound to the surface and molecules expressing the selected epitope in the sample.

No new matter is added.

Obviousness-Type Double Patenting

Claims 1, 15-16, and 18-33 have been rejected on the grounds of non-statutory, obviousness-type double patenting as being allegedly unpatentable over claims 1-16 of U.S. 7,045,286; over claims 1-2, 4, and 12-18 of U.S. 7,361,464 (formerly U.S. Serial No: 10/856,057); and claims 1-4 of U.S. 7,341,831 (formerly U.S. Serial No: 10/333,542). Claims 1-22 have been canceled. A terminal disclaimer is filed herewith to overcome these rejections.

Rejection under 35 U.S.C. § 112

Claims 1, 15-16, and 18-33 have been rejected for allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, 1st paragraph. The Examiner has asserted that these claims allegedly contain new matter, because the application as filed allegedly did not contain support for "unlabeled" RNA product. Claims 1-22 have been canceled. Applicants have amended claim 23 to remove reference to "unlabeled" RNA product and to clarify that RNA amplification produces an amplified RNA product *that is not labeled with a radioactive label or a fluorescent label*. The amendment is clearly supported by the specification at page 11, lines 24-33:

> A variety of means are available for detection of amplified products [*e.g.*, RNA product] of the epitope detector. In one embodiment, the nucleic acid sequence is detectably labeled such as with a radioactive label or a fluorescent label. *In a preferred embodiment, the nucleic acid sequence is not labeled but rather is stained by fluorescent dye.*

The italicized language supports the amendment to add "that is not labeled with a radioactive label or a fluorescent label" to the claims.

Rejection under 35 U.S.C. § 103(a) (obviousness)

Claims 1-22 have been canceled, rendering the objection moot. To the extent the Examiner would assert the cited art in a similar rejection against pending claims 23 to 33, as amended herein, Applicants would respectfully traverse. The Examiner has recognized that Applicants have argued that the words "stain" and "label" have different meanings in the claims and should be given their ordinary and customary meaning. Examiner argues that "stain" and "label" do not have definitions in the specification. Nevertheless, Examiner argues that the phrase "stain" is interpreted as set forth in the specification in which an unsymmetrical cyanine dye binds to RNA directly in the solution and then releases fluorescent signals (Examiner cites [0040] & [0041]). Examiner argues that Waggoner "discloses that cyanine dye can be used to attach to fragments of DNA or RNA to identify the presence and quantity of specific nucleotide sequence in samples of DNA or RNA (See column 8, lines 51-56)." However, the passage cited

in Waggoner states that "luminescent cyanine and related dyes can be attached to fragments of DNA or RNA. The labeled fragments of DNA or RNA can be used as fluorescent hybridization *probes* to identify the presence and quantity of specific complementary nucleotide sequences in samples of DNA or RNA." Therefore, Waggoner discloses the use of cyanine-*labeled RNA probes* for hybridization to a target sequence, and not the staining of *unlabeled* amplified RNA with cyanine dye. These facts, taken together with the other art cited by the Examiner as discussed below, fail to support a *prima facie* case of obviousness.

Applicants agree that Kacian discloses a way to detect amplified RNA from a RNA promoter-driven target oligonucleotide. Further, Applicants agree that Kacian does not disclose using an oligonucleotide linked to an antibody or fragment thereof. Applicants point out that Kacian describes detecting amplified RNA with *labeled* probes and measuring the amount of *labeled* probe that binds to the unlabeled amplified RNA. Col. 1, l. 52 to col. 2, line 3; col. 11, l. 35 to col. 14, l. 41 (Examples 1-8);col. 15, l. 11 to col. 16, l. 42 (Examples 10-12). Kacian does not teach or suggest (a) using *unlabeled* probes and (b) *staining* techniques to detect *unlabeled* amplified RNA .

Combining the teaching of Kacian with Eberwine does not cure the gaps in Kacian. Applicants agree that Eberwine discloses *labeled* amplified RNA and *unlabeled* probes that are conjugated to antibodies or portions thereof. Combining the teaching of Eberwine with Kacian would result in using unlabeled probes to detect *labeled* amplified RNA. The claims are directed to detecting *unlabeled* amplified RNA. Moreover, like Kacian, Eberwine does not teach any staining techniques to detect unlabeled amplified RNA. Accordingly, the combination of Kacian and Eberwine does not teach or suggest: (a) detecting unlabeled amplified RNA and (b) *staining* techniques to detect *unlabeled* amplified RNA.

Further addition of the teaching in Waggoner does not cure the gaps in Kacian and Eberwine. Applicants agree that Waggoner discloses cyanine dyes that can be used as labels to detect, among other things, RNA. As discussed *supra*, Waggoner discloses the use of cyanine-*labeled RNA probes* for hybridization to a target sequence, and not the staining of *unlabeled* amplified RNA with cyanine dye. Examiner argues Waggoner discloses "that cyanine dye is a

highly light absorbing dye molecule to nucleic acid and can be used for detection and quantification in very low amounts" (citing column 4, lines 35-45). However, the cited passage states "[t]his invention relates to the *covalent* reaction of highly luminescent and highly light absorbing cyanine…" (emphasis added). The use of cyanine dyes as a *stain*, as in our invention, does not involve *covalent* attachment of cyanine dyes, but rather the intercalation of the dye in the nucleic acid. (See Example 5 in Application which refers to the use of "RiboGreen reagent", which is a cyanine intercalating agent).

Finally, the addition of the teaching in Fields does not cure the gaps in Kacian, Eberwine, and Waggoner. Fields does not teach or suggest staining with dyes, using a dye to stain unlabeled amplified RNA, or quantitative methods of detecting dye staining.

The Examiner has failed to show that the cited art teaches or suggests all the elements of the claims. Thus, a *prima facie* case of obviousness has not be made.

Allowance of amended claims 23-33.

According to Examiner, claims 23-33 are free of prior art and would be allowable if amended to comply with 35 U.S.C. §112 and if a terminal disclaimer is filed to remove the objection as to obviousness-type double patenting. The claims have been modified accordingly, as discussed *supra*, and a terminal disclaimer has been filed.

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